Regarding impact of epoetin alfa on clinical end points in patients with chronic renal failure: A meta-analysis

To the Editor: We read the recent article by Jones et al [1] with interest. This meta-analysis purports to show that recombinant human erythropoietin (rHuEPO) therapy increases hemoglobin levels and reduces hospitalization rates. Unfortunately, the design of this study has several potential limitations that were not expressed in the manuscript.

First, the inclusion criteria were so exclusive that several relevant trials were not included, which may have influenced the outcome of the meta-analysis. It is noteworthy that these criteria excluded the three largest and most recent randomized studies. An example of an excluded study that might have altered the pooled effect of rHuEPO therapy is the work by Besarab et al [2].

Second (and more important), 11 of 16 trials included were nonrandomized. Because nonrandomized studies are more likely to exaggerate estimates of treatment effect [3, 4], and because inclusion of lower quality studies is known to affect the results of meta-analyses [5], we urge that the reader be circumspect of results driven by these 11 trials alone. Because the excluded trials tended to find no benefit of rHuEPO with respect to hospitalization, we wonder what the meta-analysis would have shown if all available randomized trials were considered.

In addition to these considerations about study design, we disagree with the authors' interpretation of the data. The authors state that "strong evidence" shows that rHuEPO reduces hospitalization rates, and by extension, healthcare costs. However, hospitalization costs are determined primarily by the number of hospital days, rather than by the total number of hospitalizations. While Jones et al state that the length of stay was reduced with rHuEPO therapy, its "benefit" was not statistically significant.

Although erythropoietic therapy undoubtedly raises hemoglobin levels and probably improves quality of life, the available data do not convincingly indicate that it reduces hospitalization rates in people with kidney disease. Rather, we view the information as weak and inconsistent.

We have no conflict of interest to declare.

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REFERENCES

1. JONES M, IBELS L, SCHENKEL B, *et al*: Impact of epoetin alfa on clinical end points in patients with chronic renal failure: A meta-analysis. *Kidney Int* 65:757–767, 2004
2. BESARAB A, BOLTON WK, BROWNE JK, *et al*: The effects of normal as compared with low hematocrit values in patients with cardiac disease who are receiving hemodialysis and epoetin. *N Engl J Med* 339:584–590, 1998
3. LINDE K, SCHOLZ M, MELCHART D, *et al*: Should systematic reviews include non-randomized and uncontrolled studies? The case of acupuncture for chronic headache. *J Clin Epidemiol* 55:77–85, 2002
4. GREEN SB: Patient heterogeneity and the need for randomized clinical trials. *Control Clin Trials* 3:189–198, 1982
5. MOHER D, PHAM B, JONES A, *et al*: Does quality of reports of randomised trials affect estimates of intervention efficacy reported in meta-analyses? *Lancet* 352:609–613, 1998

Editor's note: The study by Jones et al was sponsored by RW Johnson Pharmaceutical Research and Development (Raritan, NJ), a subsidiary of Johnson and Johnson, which operates companies that manufacture epoetin alfa.

Reply from the Authors

The letter from Tonelli et al [1] concerning our work reveals what we consider to be a number of misunderstandings and inconsistencies, which we would like to address.

The work is criticized as being too exclusive (i.e., omitting Besarab et al [2]), and at the same time, too inclusive in that it included studies other than randomized controlled trials (RCTs). Besarab et al [2] is actually a study of congestive heart failure patients on dialysis, and not directly relevant to our focus on chronic renal failure patients. Within this population, we sought to include all evidence available.

We must, however, strenuously reject the assertion from the letter's first paragraph "... potential limitations that were not expressed in the manuscript." The use of non-RCTs, as well as the strengths and weaknesses of the accumulated data, are all well documented in the manuscript.

We agree the impact of research design is a critically important issue. However, perhaps it was not immediately clear that Table 5 reanalyzes the data from RCTs alone. In contrast to the assertion by Tonelli et al, the estimates of effect from the RCT's are similar to, or slightly larger than, those from all studies as a whole.